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Individuals with High Bone Mass have increased progression of radiographic and clinical features of knee osteoarthritis

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Abstract

Objective: High bone mass (HBM) is associated with an increased prevalence of radiographic knee OA (kOA), characterized by osteophytosis. We aimed to determine if progression of radiographic kOA, and its sub-phenotypes, is increased in HBM and whether observed changes are clinically relevant.

Design: A cohort with and without HBM (L1 and/or total hip bone mineral density Z-score≥+3.2) had knee radiographs collected at baseline and 8-year follow-up. Sub-phenotypes were graded using the OARSI atlas. Medial/lateral tibial/femoral osteophyte and medial/lateral joint space narrowing (JSN) grades were summed and Δosteophytes, ΔJSN derived. Pain, function and stiffness were quantified using the WOMAC questionnaire. Associations between HBM status and sub-phenotype progression were determined using multivariable linear/poisson regression, adjusting for age, sex, height, baseline sub-phenotype grade, menopause, education and total body fat mass (TBFM). Generalized estimating equations accounted for individual-level clustering.

Results: 169 individuals had repeated radiographs, providing 330 knee images; 63% had HBM, 73% were female, mean(SD) age was 58(12) years. Whilst HBM was not clearly associated with overall Kellgren-Lawrence measured progression (RR=1.55[0.56,4.32]), HBM was positively associated with both Δosteophytes and ΔJSN individually (adjusted mean differences between individuals with and without HBM 0.45[0.01,0.89] and 0.15[0.01,0.29], respectively). HBM individuals had higher WOMAC knee pain scores (β=7.42[1.17,13.66]), largely explained by adjustment for osteophyte score (58% attenuated) rather than JSN (30% attenuated) or TBFM (16% attenuated). The same pattern was observed for symptomatic stiffness and functional limitation.

Conclusions: HBM is associated with osteophyte progression, which appears to contribute to increased reported pain, stiffness and functional loss.

Introduction

The relationship between bone mineral density (BMD) and osteoarthritis (OA) has been of interest for almost 50 years, since the observation that femoral heads removed during surgical repair of hip fracture were mostly unaffected by OA, indicating a potential inverse association between osteoporosis and OA (1). Since then, several large population-based studies assessing the relationship between BMD and *prevalent* and/or *incident* radiographic knee OA (kOA, usually defined as a Kellgren-Lawrence (KL) grade$\geq$2) have suggested that higher BMD is a risk factor for both (2-8). Fewer studies have assessed individual radiographic sub-phenotypes of kOA (*e.g.* osteophytes and joint space narrowing [JSN]), although in the Framingham population prevalent osteophytosis, rather than JSN, was associated with higher BMD (2) and in the Chingford study hip BMD was related to incident knee osteophytes (9).

Evidence for an association between BMD and radiographic kOA *progression* has been less consistent. Zhang *et al* found evidence for a lower odds of kOA progression with higher BMD quartile in the Framingham cohort (6), whereas Hart *et al* found lower hip BMD in women with progressive JSN from the Chingford study (9). An analysis from the Rotterdam study suggested that higher lumbar spine BMD (LS-BMD) is associated with an increased odds of kOA and osteophyte progression (10); however, this was refuted by analyses from the multicentre osteoarthritis study and the Johnston county osteoarthritis project (JoCo) (11, 12). Consistent with a protective effect of BMD on risk of kOA progression, strontium ranelate, an osteoporosis treatment reported to increase bone formation and decrease bone resorption, reduced knee cartilage loss (assessed by JSN) and western Ontario and McMaster universities OA index (WOMAC) pain score compared to placebo (13).

A novel approach to investigate the 'BMD-progressive kOA' relationship is to examine a population with generalized high BMD, as the causal direction between BMD and kOA can be inferred due to the temporal relationship (1). The UK-based High Bone Mass (HBM) study is a multi-centred study of individuals with unexplained (*i.e.* not by disorders known to artefactually elevate BMD) generalized high BMD and their unaffected relatives (14). Previous analyses have identified an increased odds of prevalent radiographic kOA in individuals with HBM, with an increased odds of osteophytes, but not JSN (15). Although previous analyses identified increased fat mass in HBM individuals (16) and adiposity as a risk factor for kOA (17), BMI adjustment only partly explained the relationship between HBM and kOA (15). The prevalence of joint replacement and NSAID use were also higher in individuals with HBM, suggestive of increased OA progression (18). We hence aimed to establish the relationship between HBM and radiographic kOA progression, particularly osteophyte progression. We further aimed to determine whether individuals with HBM have more clinical kOA symptoms and to what extent this is explained by radiographic OA sub-phenotypes.

Methods

The High Bone Mass study

Participants were recruited as part of the UK-based HBM study. Index cases were initially identified by screening Dual energy X-ray absorptiometry (DXA) databases for T and/or Z-scores≥+4. All DXA images were inspected by trained clinicians in order to exclude scans with artefactual elevation of DXA BMD (*e.g.* degenerative disease, OA, surgical/malignant artefacts). Full details of DXA database screening and participant recruitment have been published (14). Index cases passed on invitations to first-degree relatives and spouses/partners who underwent the same assessments. Participants who were aged <18, pregnant, or unable to give written informed consent were excluded. In first-degree relatives, HBM was defined as summed L1 plus TH Z-score≥+3.2. HBM in spouses was defined as per index cases. In addition to greater BMD, pQCT analyses have identified a larger periosteal circumference and evidence of a greater bone volume (19). Recruitment ran between 2005-2010. In total, 437 individuals were recruited from the eight centres participating in follow-up, of which 274 (63%) had HBM. 254 (58%) alive and consenting participants were followed up between 2017-2018; 217 (85%) completed a postal questionnaire and 174 (69%) attended for follow-up knee radiographs (*Supplementary Figure 1).*

Written informed consent was obtained in line with the declaration of Helsinki (20). The study was approved by the Bath Multi-centre Research Ethics Committee (REC reference 05/Q2001/78) and each local NHS REC. Follow-up data collection was approved by the Central Bristol REC and NHS Health Research Authority.

BMD Assessment

DXA scans were performed of the TH and LS at baseline and, after eight years follow-up, of the TH, LS and total body (TB) using standard protocols at each assessment centre. 169/174 (97%) participants re-attended their original assessment centre, limiting measurement error due to differential procedures. DXA scans were performed on Hologic scanners in Bath, Bristol, Oxford, Sheffield and St George's and GE Lunar scanners in Cambridge and Hull. Known differences in calibration exist between Hologic and Lunar (21, 22). We limited systematic bias by converting TH and LS-BMD measures to standardized BMD (sBMD) (22, 23). All images were visually inspected for positioning errors (missing body mass coded none/unilateral/bilateral) and metal artefacts (coded none/rings/large jewellery or joint replacement).

Assessment of osteoarthritis

Radiographic

Standing anteroposterior (AP), fully-extended, knee X-rays were performed at baseline and follow-up using standard protocols at each centre. To limit observer bias, all radiographs were pooled for analysis, with the reader blinded to HBM status, demographics and timepoint. Radiographs were graded for semi-quantitative OA sub-phenotypes (osteophytes/JSN, graded 0-3) and binary subchondral sclerosis using the OARSI atlas (24). Overall OA was graded using KL (25). The presence/absence of chondrocalcinosis was also assessed. Variables generated by KL grading and the OARSI atlas are summarised in *Table 1*, along with derived progression variables. Radiographs were inspected for poor image quality, rotation and/or tilt. Radiographs were viewed in open source imageJ software (26); minimal medial joint space width (mJSW) and maximum tibial plateau width were quantitatively measured using a custom-designed macro (JG). All readings were performed

by one assessor (AH) after focussed radiological training with a musculoskeletal radiologist (MW) and a rheumatologist (SAH). A random selection of 72 knees (20%) were regraded to determine intra-rater reliability and graded by a second reader (SAH) to determine inter-rater reliability. Weighted intra-rater kappa statistics for KL grade, all osteophyte and JSN variables, and unweighted kappa for chondrocalcinosis were >0.85. The intra-rater reliability kappa for subchondral sclerosis was 0.55, representing moderate agreement (27). Inter-rater weighted kappas for KL grade and all osteophyte grades were >0.8. Medial and lateral JSN and chondrocalcinosis kappas were all >0.65. The inter-rater kappa for any subchondral sclerosis was 0.47. Intraclass correlation coefficients for intra- and inter-rater reliability of quantitative measures (mJSW, maximal tibial plateau width) were $\geq$0.99.

Continuous measures of mJSW at the two timepoints were used to calculate a Reliable Change Index (RCI), which determines if the change in mJSW is meaningful over and above measurement error. Methodology for RCI calculation has been published elsewhere (28):

$$RCI = \frac{mJSW_2 - mJSW_1}{\sqrt{(\sigma_1^2 + \sigma_2^2 - 2\sigma_1\sigma_2 r(mJSW_1, mJSW_2))}}$$

The RCI is a Z-score and therefore a level exceeding 1.96 is used to denote a 'true' change over and above measurement error. A binary variable for reliable change in mJSW was therefore generated for those with an RCI$\leq$-1.96.

Clinical

Knee pain, stiffness and limitation of function were assessed by postal questionnaire at 8-year follow-up. To limit non-response bias, the questionnaire was resent if not returned within three weeks. If still unreturned after a further two weeks, a reminder telephone call was made. The WOMAC questionnaire was included in this postal questionnaire; the short

version function scale was used to limit participant burden (29, 30). The pain subscale (five questions), stiffness (two questions) and function (seven questions), each had five possible responses (none, mild, moderate, severe, extreme) scored 0-4, respectively. Missing values for pain or function questions were mean-imputed if a participant was missing one question on the pain scale and $\leq$3 on the function scale. Average scores were calculated for each subscale and scaled to give a score ranging from 0-100, with 0 representing no pain, stiffness or limitation of function (31). Health-related quality of life (HR-QoL) was determined using the EuroQol EQ-5D questionnaire (32). Responses to the five questions were converted to index values using the crosswalk index value calculator and UK value set (33). If an individual was missing a response for any domain, an index value was not calculated.

Covariate data

At baseline, structured interview and clinical examination determined participant characteristics including age, menopausal status and standing height. Highest educational attainment (as a marker of socioeconomic status [SES]), determined by follow-up questionnaire, was categorised as up to GCSE/O-Level (or equivalent), A-Level (or equivalent) and degree level or above. Total body fat mass (TBFM) was assessed by TB DXA scans.

Statistical analysis

Associations between HBM status and binary OA incidence and progression variables were determined by multivariable poisson regression, to generate an estimate of the risk ratio (34), using generalized estimating equations (GEE) to account for clustering in knee radiographs per person.. Associations with continuous osteophyte and JSN progression

variables were determined by multivariable GEE linear regression with robust standard errors to account for any non-normal distributions in outcome variables. Betas from analysis of continuous variables represent the difference in mean outcome between those with and without HBM (e.g. a beta of 1 for Δosteophyte represents a 1-point greater increase in summed osteophyte score). Osteophyte and/or JSN scores of 0 at baseline were included in analyses. Analyses were initially performed unadjusted (model 1), then adjusted for age and sex (and baseline sub-phenotype score for continuous outcomes) (model 2), then additionally adjusting for height, menopause and education (model 3). Our previous analyses have identified that HBM is associated with increased TBFM, with evidence suggesting this is a consequence rather than a cause of HBM (16). Therefore, adiposity is predicted to be on the causal pathway in these analyses, hence a possible mediating effect was determined by additional adjustment for TBFM in model 4. All analyses were restricted to individuals with complete data for model 4. Statistical analysis was performed in Stata version 15 (Statacorp, USA) and R version 3.5.1. In line with the recommendation of the American Statistical Association, we base our interpretation of the results on the size of associations and their confidence intervals (CIs), rather than *p*-values (35).

Sensitivity analyses

Joints with knee replacements (TKR) were excluded; however, as TKR were likely performed due to severe OA, analyses of progressive OA were repeated assuming knees with KL$\geq$2 and TKR at follow-up had progressive OA. Those with a baseline KL score<2 and TKR at follow-up were coded as both incident and progressive OA cases. A person-level analysis, using variables for OA progression in either knee or the highest value of the two knees for osteophyte/JSN scores was performed. Individuals reporting a 'cartilage operation' (12

knees), knee lavage/washout/arthroscopy (16 knees) or a steroid injection (9 knees) by questionnaire were removed. A model adjusting for metal artefacts on DXA scans, and analyses removing individuals with positioning errors leading to under-measurement of TBFM by DXA (10 knees) were performed. We further adjusted for maximum tibial plateau width to determine whether BMD, rather than bone size, explained any associations observed. Finally, to check conclusions were valid despite skewed continuous outcomes, all linear analyses were repeated using a Poisson model.

Results

Characteristics of the study population

Baseline and follow-up radiographs were available from 169 individuals, 63% of whom had HBM. Mean follow-up time was 8.3 years (SD 1.0), which did not differ between individuals with and without HBM (*Table 2*). Those with follow-up data were more commonly female, premenopausal and physically active and less likely to smoke and have diabetes than individuals not followed-up, although the proportion of females in the baseline and follow-up populations was similar (65 *vs* 73%, respectively) (*Supplementary Table 1*). No differential loss-to-follow-up between HBM cases and their relatives was evident; the baseline prevalence of kOA, kOA sub-phenotypes, and TKR were similar in those with and without follow-up radiographs.

As expected, based on baseline observations, individuals with HBM were more commonly female (84% *vs* 55%), postmenopausal (74% *vs* 53%) with greater baseline BMD (mean TH-BMD 1.25 *vs* 0.97g/cm^2) and BMI (30.4 *vs* 27.7kg/m^2) than individuals without HBM (*Table 2*). Overall, changes in TH and LS-BMD over eight years were minimal; more marked declines in TH-BMD in HBM individuals (-0.44 *vs* -0.09% per year) were explained by older age of HBM cases in regression analyses.

HBM and the incidence and progression of OA overall

The prevalence of radiographic kOA (KL$\geq$2) was higher at both baseline and follow-up in individuals with HBM compared with those with normal BMD (34 *vs* 18% at baseline,50 *vs* 27% at follow-up, *Table 3*). After adjustment (model 4) a weak trend was seen towards more incident (RR=1.71[0.88,3.33]) and progressive (RR=1.55[0.56,4.32]) kOA in HBM

individuals, but confidence intervals (CIs) were wide. Combining incident and progressive OA as a single variable, we observed increased risk of incident/progressive OA in individuals with HBM (OR=1.76[1.03,3.02]).

HBM and the incidence and progression of OA sub-phenotypes

Individuals with HBM had greater osteophyte development (Δosteophyte: change in summed osteophyte score since baseline, reflecting incidence and/or progression) than individuals without HBM (unadjusted mean difference=0.65[0.22,1.08],*p*=0.003, *Figure 1*). Adjustment for age, sex, baseline osteophyte score, menopause, SES, height and TBFM explained approximately one-third of this relationship (fully-adjusted mean difference=0.44[0.02,0.87],*p*=0.041). Furthermore, a strong association between *baseline* TH-BMD and osteophyte development was observed (β=0.28[0.05,0.51],*p*=0.019, β represents the change in Δosteophyte score per SD increase in TH-BMD). No association between *change* in TH-BMD and osteophyte development was evident (*Supplementary Figure 2*).

Development of JSN was more common in individuals with HBM, independent of TBFM, but this association (mean difference=0.16[0.02,0.29],*p*=0.028) was less pronounced than that seen for osteophyte development. When JSN development was measured using reliable change in mJSW, HBM individuals had an increased risk of 'true' JSN, independent of TBFM (RR=6.94[1.10,43.6],*p*=0.039), although CIs were wide reflecting the rarity of this outcome. Whilst *baseline* TH-BMD was associated with increased risk of reliable change in mJSW (fully-adjusted RR=2.59[1.29,5.19],*p*=0.007), *change* in TH-BMD between baseline and follow-up was not (*Supplementary Figure 2*). At both baseline and follow-up, the prevalence

of chondrocalcinosis and subchondral sclerosis were similar in those with and without HBM *(Supplementary Table 2)*, as was the incidence of both *(Figure 1)*.

HBM and clinical features of OA

Before adjustment (model 1), individuals with HBM had approximately 10-point higher WOMAC scores (β_{pain}=11.2[5.4,17.0], $\beta_{stiffness}$=11.0[4.5,17.5] and $\beta_{function}$=9.7[4.8,14.7], all p<0.001), compared to relatives with normal BMD. In analyses adjusted for age, sex, height, menopause and SES (model 3), these associations persisted with mean differences in WOMAC scores all >6.5/100 (*Figure 2)*. Further adjustment for TBFM or JSN score attenuated these associations by approximately 20%, whereas adjustment for follow-up osteophyte score attenuated these associations by >50%. The same pattern was observed for HR-QoL, with HBM individuals having a lower HR-QoL compared to relatives without HBM ($\beta_{model\ 3}$=-0.07[-0.13,-3.90x10^{-3}]), with further adjustment for osteophyte scores attenuating this association by a greater proportion than TBFM or JSN adjustment (*Figure 2*).

Investigating dose-response relationships between BMD and OA outcomes

Baseline TH-BMD Z-score was categorized into quartiles in both the HBM and non-HBM populations. Osteophyte development increased with increasing TH-BMD quartile in the HBM population (p for trend=0.043), until quartile 4, where mean Δosteophyte score appeared to plateau; no such relationship was seen in the non-HBM group (*Figure 3A).* No evidence of a dose-response relationship between TH-BMD and ΔJSN was detected (*Figure 3B)*. A clear dose-response relationship between TH-BMD and WOMAC pain scores was observed in individuals with HBM (p for trend<0.001) but not the non-HBM group (*Figure 3C).*

Sensitivity analyses

Findings were consistent when analyses were performed at a person-level, although CIs widened. Including ten additional knees with baseline OA and incident TKR strengthened the magnitude of the association between HBM and OA progression (fully-adjusted RR=1.99 [0.87,4.54]), but CIs were still wide as only 86 individuals had OA at baseline (*i.e.* could progress). Including three knees, with KL<2 at baseline and TKR at follow-up, as incident OA weakened evidence for an association between HBM and incident OA (RR=1.53[0.82,2.87]). Excluding five individuals who attended a different study site for their follow-up radiographs did not alter findings, nor did adjustment for metal artefacts or removal of individuals with DXA positioning errors. Excluding knees of individuals self-reporting a prior cartilage operation or knee washout/lavage/arthroscopy marginally strengthened the association between HBM and Δosteophytes, but otherwise conclusions were unchanged (*Supplementary Figure 3*). Additional adjustment for maximum tibial plateau width did not attenuate the association between HBM and osteophyte development. Repeating analyses using a Poisson regression model did not alter conclusions drawn.

Discussion

This study is the first to evaluate progression of sub-phenotypes of kOA in a population with HBM. Both initial appearance and subsequent growth of osteophytes are increased in individuals with HBM compared to those with normal BMD. Furthermore, we have shown that HBM individuals suffer a greater burden of clinical symptoms of kOA (pain, stiffness and functional limitation), with poorer HR-QoL, with symptoms largely explained by adjustment for osteophytosis severity. Our results are consistent with the one general population study which identified a positive relationship between LS-BMD and knee osteophyte progression (10).

The relationship between high BMI and kOA is widely acknowledged (17, 36).HBM is characterised by increased TBFM (16), with development of HBM likely preceding fat mass accumulation due to its genetic origin (37).TBFM could mediate the association between HBM and OA progression through increased joint loading or other metabolic pathways. However, the associations we observed between HBM and greater osteophyte development were independent of TBFM. This finding is consistent with one earlier population-based study of North American women in whom those with low BMD and low BMI had the lowest KL grades, those with high BMD and high BMI had the highest KL grades, and those with low BMI and high BMD had similar KL grades to those with high BMI and low BMD, suggesting that the underlying biological pathway leading to increased osteophyte development in individuals with higher BMD is independent of adiposity (3).

Our previous analyses of this HBM population identified an increased presence of enthesophytes, reflecting their 'bone-forming' phenotype (38). Increased osteophyte development over eight years provides further evidence for this phenotype. As both BMD

and kOA are highly heritable (39, 40), one potential explanation for this 'bone-forming' phenotype is pleiotropy, whereby the same genetic variants contribute to both phenotypes: genetic analyses in the Osteoarthritis Initiative and JoCo populations identified a positive association between four BMD-associated genetic single nucleotide polymorphisms (SNPs) and kOA (41). Such pleiotropy could reflect a causal pathway between BMD and kOA, supported by a recent mendelian randomisation (MR) study (42), or shared underlying biological pathways contributing to both phenotypes. Individuals with HBM have an over-representation of common BMD-associated variants, including those which annotate to bone-forming pathways, e.g.Wnt signalling (37), also linked to OA (43). Although, a more recent genome-wide analysis did not find evidence for a genetic correlation between FN-BMD and kOA (44). Differences in subchondral bone texture may explain the positive, albeit weaker, association between HBM and JSN progression (1). Higher trabecular number and thickness plus reduced trabecular separation in subchondral bone have been linked to medial JSN progression (45). Individuals with HBM have increased trabecular density at both the tibia and radius (19); it is currently unknown whether HBM individuals have altered subchondral trabecular bone texture predictive of JSN progression.

In contrast to our analysis, Zhang *et al* found that risk of kOA progression declined with increasing BMD in the Framingham cohort (6). One possible explanation for this disparity is that authors defined kOA progression as change in KL score in those with prevalent kOA at baseline. To have KL$\geq$2, an individual must present with osteophytes and to increase KL grade, JSN must occur (25). Therefore, progression from KL=2 to KL=3 relies solely on incident JSN, not worsening of osteophyte grade. Using an increased KL grade to define progression is also vulnerable to bias due to a ceiling effect, as those with a KL grade of 4 at baseline cannot progress. Another potential explanation for the observed inverse

association in the Framingham study is 'collider bias', as analyses were restricted to those with kOA at baseline (*i.e.* case only), thereby potentially inducing a negative correlation between BMD and any other variable that influences incident OA. If any such variable is also associated with progression and is not appropriately controlled for in the analysis, a 'backdoor pathway' from high BMD to kOA progression can be induced. This can manifest as a negative association, when in fact there is none, or even a true positive association (46).

Our finding that individuals with HBM suffer increased clinical symptoms of OA, independent of TBFM, is consistent with a recent MR analysis which identified a causal relationship between FN-BMD and hospital-diagnosed kOA, even after excluding BMI-associated SNPs from the instrument (42). OA is frequently diagnosed clinically due to symptoms, such as pain, rather than by radiography (47) and therefore hospital-diagnosed kOA is likely to reflect symptomatic OA, confirmed by radiographic changes. One Bradford-Hill criterion supporting causal inference is a dose-response relationship (48); we found increased WOMAC pain scores with increasing TH-BMD quartiles in HBM individuals. The observation that adjustment for osteophyte severity at follow-up attenuated the association between HBM and pain to a greater extent than adjustment for JSN is consistent with the findings of Cicuttini *et al,* who observed that the odds of ever having knee pain was increased in middle-aged women with osteophytes compared to those without osteophytes, and this association was stronger than the association between knee JSN and knee pain (49). However, Neogi *et al* found that JSN, rather than osteophytes, was more strongly related to knee pain in individuals with knees discordant for pain (50).

Strengths and limitations

The HBM study constitutes a large cohort of individuals with relatively rare, unexplained, generalized HBM (14). Detailed data were collected at baseline and follow-up allowing for adjustment for potential confounders. We analysed change in OA sub-phenotypes separately as well as using KL score, which allowed us to detect the strong relationship with osteophyte development and the weaker relationship with change in JSN. We analysed change in osteophytes and JSN as continuous measures, increasing statistical power to detect associations, and reducing the possibility of a ceiling effect by increasing the range of possible values from 0-6 for JSN and 0-12 for osteophytes. However, this study has some limitations. The method of identifying individuals from NHS DXA databases ascertained an older population such that a relatively large proportion were unable to be followed-up due to death or poor health. X-rays and DXA scans were performed using standard protocols at each centre but were not cross-calibrated. Sample size restrictions meant we could not evaluate change in osteophyte score in individuals with osteophytes at baseline (progression) separately from those with no osteophytes at baseline (incidence). A small number of individuals (0.3%) had a baseline summed osteophyte score of at least 10, almost the maximum score, meaning progression of summed score was limited. All those with a score $\geq$10 at baseline were HBM cases, meaning the relationship between HBM and osteophyte progression may have been underestimated due to a possible ceiling effect. Baseline and follow-up radiographs were not read paired and we did observe a few negative scores for change in osteophytes (<4%) and change in JSN (<2%), which were included in analyses. Removing these values as 'measurement error' could have biased results as there is likely to be the same proportion of measurement error overinflating change, for which we would not be able to account. Reassuringly, the small proportion with negative values did not differ between HBM and relatives. Radiographic grading of OA sub-phenotypes is

subjective, which we limited using an established atlas (24), and our intra-rater and inter-rater reliability were substantial for all variables except subchondral sclerosis (27). WOMAC scores were only collected at follow-up and therefore we were not able to assess change in symptoms. Finally, as this is an extreme population with a female majority, generalizability is limited.

Conclusions

We have found evidence that individuals with HBM have increased osteophyte development over eight years, independent of fat mass, and a greater number and/or size of osteophytes is associated with greater pain, stiffness and functional limitation and reduced HR-QoL. Future analyses are planned to determine the underlying biological pathways leading to this increased osteophyte development. It is hoped that understanding of such pathways will offer opportunities to identify targets for therapies aimed at reducing the clinical symptoms of OA.

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Author contributions

Conception and design: JHT and CLG. Analysis and interpretation of the data: AH, JHT, CLG. Drafting of the article: AH and CLG. Critical revision of the article for important intellectual content: all authors. Final approval of the article: all authors. Provision of study materials or patients: EM, MW, MKJ, KESP, MA, KM, TA, JHT. Statistical expertise: LP, RG, JHT, CLG. Obtaining of funding: EM, MKJ, KESP, JHT, CLG. Technical support: SAH, MW, JG, JVM. Collection and assembly of data: AH, SAH, EM, MW, MKJ, KESP, MA, KM, TA, JHT, CLG. AH and CLG will serve as guarantors for the contents of this paper.

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Competing interests

The authors have no competing interests to disclose.

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Tables

Table 1: Variables generated by Kellgren-Lawrence grading and the OARSI atlas and variables derived for analysis

Variable	Grading	Variable used in analysis
Osteoarthritis (KL grade)	0-4	Progressive OA: KL grade ≥2 at baseline and an increase in grade at follow-up Incident OA: KL grade <2 at baseline and ≥2 at follow-up
Osteophytes		Osteophyte progression: Sum of all semi-quantitative osteophyte grades at follow-up – sum at baseline
Medial femoral	0-3	
Lateral femoral	0-3	
Medial tibial	0-3	
Lateral tibial	0-3	
JSN		JSN progression: Sum of both semi-quantitative JSN grades at follow-up – sum at baseline
Medial	0-3	
Lateral	0-3	
Subchondral sclerosis		Incident sclerosis: no sclerosis (medial or lateral) at baseline and any sclerosis at follow-up
Medial	0, 1	
Lateral	0, 1	
Chondrocalcinosis	0, 1	Incident chondrocalcinosis: no chondrocalcinosis at baseline and chondrocalcinosis at follow-up
mJSW	continuous	Change in mJSW: mJSW at follow-up – mJSW at baseline Reliable change in mJSW: Reliable change index ≤-1.96

Abbreviations: OARSI: osteoarthritis research society international; KL: Kellgren-Lawrence; JSN: joint space narrowing; mJSW: medial minimal joint space width

Table 2: Characteristics of the study population

	All N=169	HBM Individuals N=107	Non-HBM Relatives N=62	*p* value for difference
		N (%)		
Female gender	124 (73.3)	90 (84.1)	34 (54.8)	7.22×10^{-5}
Postmenopausal at baseline	85 (68.5)	67 (74.4)	18 (52.9)	0.037
Menopause transition during follow-up	13 (10.8)[a]	7 (8.1)	6 (17.7)	0.131
History of ERT use[b]	55 (45.5)[c]	44 (50.0)	11 (33.3)	0.151
History of smoking[b]	81 (50.6)	49 (49.0)	32 (53.3)	0.596
Alcohol consumption[b]				0.037
Never	15 (9.0)	7 (6.7)	8 (12.9)	
Monthly or less	60 (35.9)	46 (43.8)	14 (22.6)	
Weekly	49 (29.3)	29 (27.6)	20 (32.3)	
Daily/ most days	43 (25.8)	23 (21.9)	20 (32.3)	
Physical activity at baseline				0.453
Low	19 (11.6)[d]	11 (10.8)	8 (12.9)	
Medium	58 (35.4)	33 (32.4)	25 (40.3)	
High	87 (53.0)	58 (56.9)	29 (46.8)	
Education[e]				0.061
Up to GCSE/ O level	67 (41.4)	50 (48.1)	17 (29.3)	
A level or equivalent	37 (22.8)	22 (21.2)	15 (25.9)	
Degree or equivalent	58 (35.8)	32 (30.8)	26 (44.8)	
		Mean (SD)		
Age at baseline, years	57.7 (12.3)	58.4 (12.6)	56.4 (11.7)	0.303
Age at follow-up, years	65.9 (12.4)	66.7 (12.7)	64.7 (11.8)	0.312
Height at baseline, cm	167.7 (9.2)	166.5 (8.0)	169.8 (10.6)	0.036
Weight at baseline, kg	82.6 (17.6)	84.1 (17.6)	80.0 (17.4)	0.146
BMI at baseline (kg/m^2)	29.4 (5.9)	30.4 (6.2)	27.7 (5.0)	0.003
TBFM (kg)[f]	32.1 (10.9)	33.2 (11.3)	30.0 (10.0)	0.076
Baseline TH Z-Score	2.03 (1.50)	2.96 (0.95)	0.46 (0.80)	8.55×10^{-39}
Baseline TH-BMD, g/cm^2 [g]	1.15 (0.19)	1.25 (0.14)	0.97 (0.13)	1.03×10^{-26}
Change in TH-BMD, % per year[g]	-0.31 (0.92)	-0.44 (0.94)	-0.09 (0.84)	0.020
Baseline L1 Z-Score	2.47 (1.96)	3.64 (1.25)	0.44 (1.14)	4.20×10^{-37}
Baseline L1-BMD, g/cm^2 [h]	1.26 (0.22)	1.38 (0.15)	1.06 (0.14)	1.39×10^{-29}
Change in L1-BMD, % per year[h]	0.02 (1.19)	0.02 (1.24)	0.02 (1.09)	0.994
Follow-up time, years	8.3 (1.0)	8.3 (0.7)	8.2 (1.3)	0.871

a: N=120 (86 HBM, 34 relatives); b: past or present (assessed at follow-up); c: N=112 (81 HBM, 31 relatives) c: N=121 (88 HBM, 33 relatives); d: N=164 (102 HBM); e: N=162 (104 HBM, 58 relatives); f: assessed at follow-up; g: N=166 (104 HBM); h: N=167 (105 HBM)

Abbreviations: ERT: estrogen replacement therapy; BMI: body mass index; TBFM: total body fat mass; BMD: bone mineral density; TH: total hip; L1: 1st lumbar vertebra.

Table 3: Prevalence of radiographic and clinical OA sub-phenotypes in the study population

	All knees		HBM knees		Non-HBM knees		
	Total N	**N (%)**	**Total N**	**N (%)**	**Total N**	**N (%)**	
OA (KL≥2)							
Baseline	330	94 (28.48)	209	72 (34.45)	121	22 (18.18)	**
Follow-up	312	129 (41.35)	194	97 (50.00)	118	32 (27.12)	***
Incident	232	55 (23.71)	135	41 (30.37)	97	14 (14.33)	**
Progressive	80	24 (30.00)	59	19 (32.20)	21	5 (23.81)	
Knee replacement							
Baseline	337	7 (2.08)	214	5 (2.34)	123	2 (1.63)	
Follow-up	337	25 (7.42)	214	20 (9.35)	123	5 (4.07)	
Incident	330	18 (5.45)	209	15 (7.18)	121	3 (2.48)	
Subchondral sclerosis							
Baseline	330	6 (1.82)	209	4 (1.91)	121	2 (1.65)	
Follow-up	312	19 (6.09)	194	11 (5.67)	118	8 (6.78)	
Incident	310	17 (5.48)	193	10 (5.18)	117	7 (5.98)	
Chondrocalcinosis							
Baseline	330	18 (5.45)	209	11 (5.26)	121	7 (5.79)	
Follow-up	312	39 (12.50)	194	26 (13.40)	118	13 (11.02)	
Incident	297	26 (8.75)	186	20 (10.75)	111	6 (5.41)	
Reliable change in mJSW (RCI≤-1.96)	299	16 (5.4)	189	14 (7.41)	110	2 (1.82)	*
Osteophyte score							
Baseline	330		209		121		**
0		236 (71.52)		137 (65.55)		99 (81.82)	
1-4		79 (23.94)		59 (28.23)		20 (16.53)	
≥5		15 (4.55)		13 (6.22)		2 (1.65)	
Follow-up	312		194		118		***
0		183 (58.65)		97 (50.00)		86 (72.88)	
1-4		97 (31.09)		69 (35.57)		28 (23.73)	
≥5		32 (10.26)		28 (14.43)		4 (3.39)	
Delta	312		194		118		***
<1		211 (67.63)		115 (59.28)		96 (81.36)	
1		33 (10.58)		25 (12.89)		8 (6.78)	
>1		68 (21.79)		54 (27.84)		14 (11.86)	
JSN score							
Baseline	330		209		121		
0		283 (85.76)		177 (84.69)		106 (87.60)	
1-2		43 (13.03)		29 (13.88)		14 (11.57)	
≥3		4 (1.21)		3 (1.44)		1 (0.83)	
Follow-up	312		194		118		
0		244 (78.21)		146 (75.26)		98 (83.05)	
1-2		59 (18.91)		40 (20.62)		19 (16.10)	
≥3		9 (2.88)		8 (4.12)		1 (0.85)	
Delta	312		194		118		*
<1		267 (85.58)		162 (83.51)		105 (88.98)	
1		35 (11.22)		22 (11.34)		13 (11.02)	
>1		10 (3.21)		10 (5.15)		0 (0.00)	
	Total N	**Median (IQR)**	**Total N**	**Median (IQR)**	**Total N**	**Median (IQR)**	

WOMAC at follow-up							
Pain	154	5 (0, 30)	100	12.5 (0, 40)	54	0 (0, 10)	***a
Stiffness	153	12.5 (0, 37.5)	99	25 (0, 50)	54	0 (0, 25)	**a
Function	153	3.6 (0, 28.6)	99	10.7 (0, 39.3)	54	0 (0, 17.9)	**a
	Total N	**Mean (SD)**	**Total N**	**Mean (SD)**	**Total N**	**Mean (SD)**	
mJSW							
Baseline	328	4.98 (1.17)	209	5.02 (1.18)	119	4.92 (1.14)	
Follow-up	300	4.84 (1.39)	188	4.89 (1.53)	112	4.76 (1.11)	
Delta	298	-0.206 (1.15)	188	-0.241 (1.27)	110	-0.144 (0.90)	

*: $p<0.05$; **:$p<0.01$, ***:$p<0.001$

a*: P* values for skewed outcomes were generated from a Mann-Witney U test.

Abbreviations: HBM: high bone mass; KL: Kellgren-Lawrence; JSN: joint space narrowing; RCI: reliable change index; mJSW: medial minimal joint space width

Figure legends

Figure 1: Associations between HBM status and incident and progressive OA sub-phenotypes

Points for continuous outcomes represent the difference in mean outcome between individuals with and without HBM (For example, a beta of for Δosteophyte would represent a 1 point greater increase in summed osteophyte score, which is the equivalent of the appearance of one additional osteophyte over 8 years or the increase in size of an osteophyte already present). Points for binary outcomes represent the risk ratio for individuals with HBM compared to their relatives with normal BMD

Model 1: unadjusted, Model 2: adjusted for age and sex (plus baseline score for continuous outcomes), Model 3: adjusted for age, sex, height, SES and menopause (plus baseline score for continuous outcomes), Model 4: Model 3 plus TBFM

N_{mJSW}=278; $N_{chondrocalcinosis}$=274; $N_{subchondral\ sclerosis}$=287. Abbreviations: JSN: joint space narrowing; mJSW: medial minimal joint space width

Figure 2: Associations between HBM status and WOMAC pain, stiffness and function subscale scores and health-related quality of life

Points represent the mean difference in WOMAC scores between individuals with HBM and relatives/ spouses without HBM. Person-level analysis, accounting for clustering in families. Follow-up osteophyte and JSN score is the highest of the two knees. Model 1: unadjusted, Model 3: adjusted for age, sex, height, SES and menopause. $N_{stiffness/function}$=148

Figure 3: Association between quartiles of total hip BMD Z-score and (A) change in osteophyte score, (B) change in JSN score and (C) WOMAC pain scores in individuals with HBM (top) and relatives without HBM (bottom)

Results for mean osteophyte scores are based on GEE-linear regression accounting for two knees per individual.

Abbreviations: TH-BMD: total hip bone mineral density